Acute poststaphylococcal glomerulonephritis superimposed on diabetic glomerulosclerosis

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CASE PRESENTATION

A 67-year-old Caucasian male presented with a 1-week history of productive cough and shortness of breath. He was found to have left lower lobe pneumonia, was admitted to the hospital, and was started on antibiotics. He developed acute renal failure shortly after admission with an increase in serum creatinine from 1.4 mg/dl (124 μmol/l) on hospital day 1 to 2.0 mg/dl (177 μmol/l) on day 4 to 7.0 mg/dl (619 μmol/l) on day 20.

Past medical history was significant for diabetes mellitus type II for 7 years with neuropathy, but without diabetic retinopathy. He also had history of coronary artery disease status-post coronary artery bypass graft, mitral valve regurgitation status-post replacement, atrial fibrillation, longstanding hypertension that was well-controlled on medications, and chronic renal insufficiency with a baseline serum creatinine of 1.4 mg/dl (124 μmol/l). He denied alcohol or IV drug use. He had no family history of renal disease. His medications on admission included furosemide, low dose aspirin, coumadin, glyburide, and metoprolol. He had 1+ lower extremity edema bilaterally. There were no cutaneous findings.

Laboratory results during hospitalization were as follows: hematocrit 38%, white blood count 14 600/mm^3 (normal range 4300–10 800/mm^3), platelets 243 $\times$ 10^9/l (normal range 150–500 $\times$ 10^9/l), urine protein 150 mg/day, and serum albumin 3.6 g/dl (36 g/l) (normal range 3.5–4.9 g/dl (35–49 g/l). He had normal serum electrolytes, a depressed C3 complement level, and normal C4. All other serologies were negative or normal including anti-nuclear antibody, anti-double-stranded DNA antibody, hepatitis B surface antigen, hepatitis C antibody, antistreptolysin O antibody, serum cryoglobulin, antineutrophil cytoplasmic antibody, and anti-glomerular basement membrane (GBM) antibody. There was no M spike on serum protein electrophoresis. Urinalysis showed trace protein, numerous red blood cells/high-power field (hpf), 5–10 white blood cells/hpf, and several red blood cell casts. Sputum and blood cultures were positive for methicillin-resistant *Staphylococcus aureus*. Urine culture was negative. Chest X-ray showed consolidation of the left lower lobe of lung. The kidneys were normal in size by ultrasound. Hemodialysis was initiated and a renal biopsy was performed on hospital day 20.

RENAL BIOPSY FINDINGS

The kidney biopsy contained 11 glomeruli for light microscopy, one of which was globally sclerotic. Glomeruli appeared markedly enlarged and diffusely hypercellular with accentuated lobularity (Figure 1a). There was marked diffuse and global endocapillary proliferation including numerous infiltrating neutrophils with fewer monocytes. One glomerulus displayed segmental fibrinoid necrosis. Mesangial areas were expanded by mild to moderate increase in mesangial matrix, forming segmental nodules (Figure 1b). The GBM appeared mildly and diffusely thickened with a uniform texture. Trichrome stain delineated segmental mesangial and subendothelial fuchsinophilic deposits. No crescents were seen. Approximately 25% of the cortex had patchy interstitial expansion by edema and mild inflammatory infiltrates of lymphocytes, monocytes, and plasma cells. Proximal tubular cells contained focal protein and lipid resorption droplets. There was focal, mild tubular atrophy, and interstitial fibrosis involving $<$10% of the cortex. There was mild to moderate arterio- and arteriolosclerosis and mild arteriolar hyalinosis.

Three glomeruli were studied by immunofluorescence and showed 3+ granular global mesangial and peripheral capillary wall staining for IgA (Figure 1c) and C3, with 1+ positivity for IgG, trace C1q, 1–2+ κ, and 3+ λ. There was also 1+ linear staining for albumin involving glomerular and tubular basement membranes. Staining for IgM was negative.

On ultrastructural examination, the mesangial areas were expanded by a moderate increase in mesangial cells and matrix with focal nodular mesangial sclerosis. Glomerular

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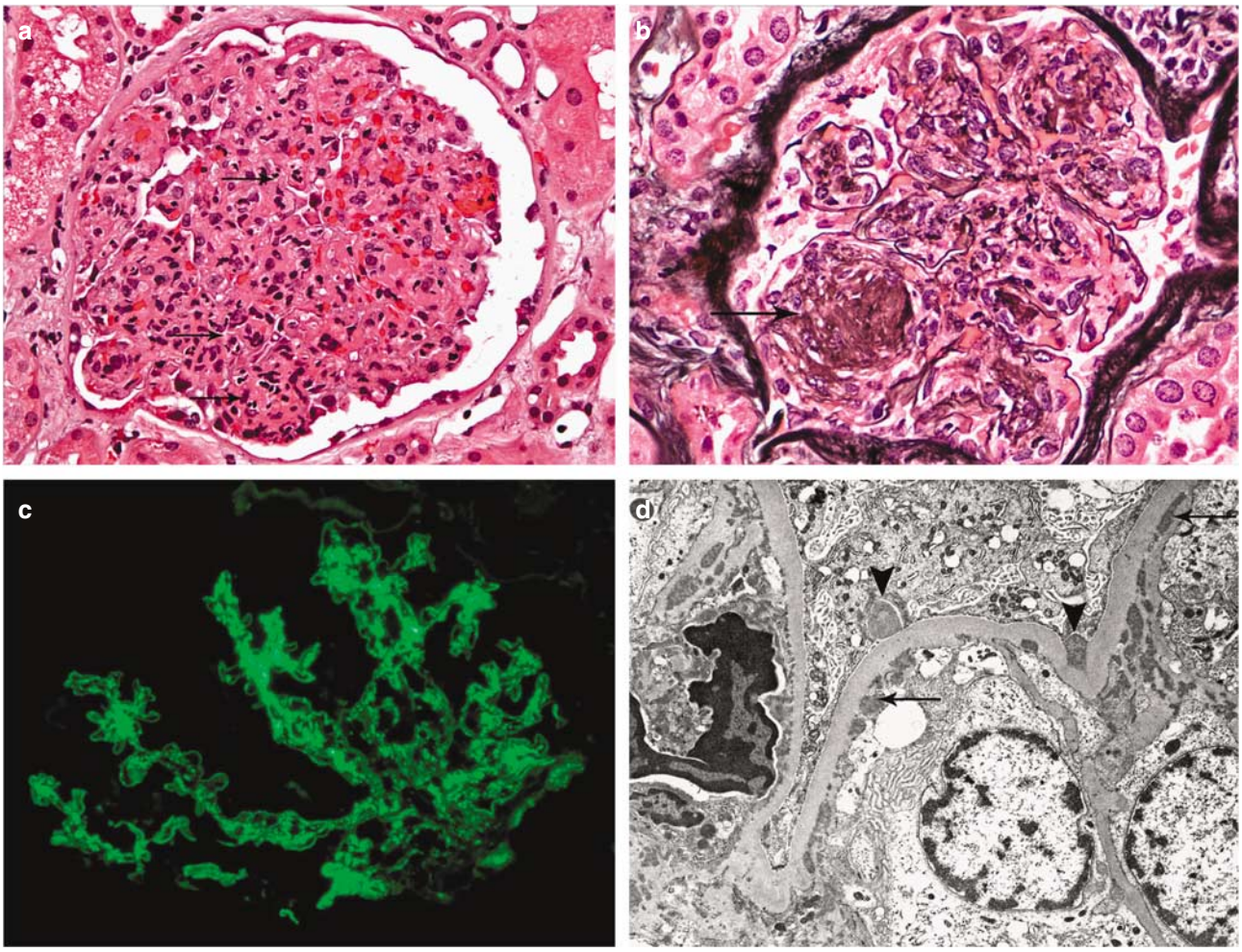

Figure 1 | Renal biopsy findings. (**a**) A glomerulus shows diffuse endocapillary proliferation with many infiltrating neutrophils (arrows). (Hematoxylin & eosin, original magnification × 400). (**b**) Underlying changes of nodular diabetic glomerulosclerosis are apparent with the Jones methenamine silver stain. The arrow highlights an argyrophilic nodule of mesangial sclerosis (original magnification × 600). (**c**) Immunofluorescence staining for IgA reveals high intensity global positivity in a mesangial distribution, with less prominent staining of peripheral capillary walls (original magnification × 250). (**d**) On ultrastructural evaluation, prominent subendothelial (arrows) and rare subepithelial 'hump-shaped' (arrowhead) electron dense deposits are seen. There is mild global thickening of the GBM, typical of diabetic glomerulosclerosis (original magnification × 4000).

capillary lumina were narrowed or occluded by severe endocapillary proliferation including numerous infiltrating neutrophils. There were abundant large mesangial and subendothelial electron dense deposits (Figure 1d). The glomerular basement membranes were diffusely and moderately thickened. Two glomerular capillaries contained isolated small hump-shaped subepithelial electron dense deposits. No endothelial tubuloreticular inclusions were seen. There was extensive effacement of foot processes involving approximately 80% of the glomerular capillary surface area.

FINAL DIAGNOSIS

Diffuse endocapillary proliferative and exudative glomerulonephritis, severe, consistent with IgA-dominant acute poststaphylococcal glomerulonephritis, superimposed on mild to moderate nodular diabetic glomerulosclerosis.

CLINICAL FOLLOW-UP

The patient was maintained on antibiotics, continued to have proteinuria and hematuria, and remained dialysis dependent. He died of sepsis 3 months following the renal biopsy.

DISCUSSION

Acute post-infectious glomerulonephritis (APIGN) is mainly a disease of children. It usually develops following streptococcal upper respiratory tract or skin infections. Adult APIGN is most common in diabetic, alcoholic, and intravenous drug-abusing patients.[1] In developed countries, the responsible bacteria for adult APIGN are now more commonly *Staphylococcus* or Gram-negative bacteria than *Streptococcus*.[1]

Two pathological patterns of glomerulonephritis associated with staphylococcal infection are well-defined. Glomerulonephritis secondary to *S. aureus* infection, whether

occurring after skin infection, deep-seated abscesses, or endocarditis, exhibits a histological pattern identical to acute poststreptococcal glomerulonephritis. Typical findings include diffuse endocapillary proliferative and exudative glomerulonephritis on light microscopy, C3-dominant deposits with or without IgG co-deposition on immunofluorescence, and subepithelial hump-shaped deposits on electron microscopy. In contrast, shunt nephritis associated with *S. epidermidis* most commonly displays a pattern indistinguishable from type I membranoproliferative glomerulonephritis, with varying degrees of mesangial interposition and duplication of GBM and subendothelial deposits that stain for C3 and IgM or C3 and IgG.

In recent years, a third form of *Staphylococcus*-associated glomerulonephritis characterized by IgA-dominant or co-dominant glomerular deposits, resembling IgA nephropathy, has been increasingly recognized. There are 22 cases of this entity reported in the English literature, 15 of which were reported in the last 4 years.[2–8] Two-thirds of these cases were from the US and the remaining third were reported from Japan. Table 1 summarizes the clinical and pathological findings of all 22 cases. All patients were adults and 18 (82%) were 50 years or older. Predisposing factors to infection included diabetes in seven patients, malignancy in three, and poor nutrition in one. The sites of staphylococcal infection were cutaneous in seven patients, deep-seated abscesses in seven, surgical wounds in four, pneumonia in two, endocarditis in one, and a joint infection in one. Twelve patients (55%) had methicillin-resistant *S. aureus*, 6 (27%) had methicillin-sensitive S. *aureus*, and three (14%) had *S. epidermidis*. The *Staphylococcus* species was not specified in one patient. The clinical onset of infection varied from less than a week to 16 weeks before the onset of renal manifestations. The majority of patients presented with renal failure (acute or rapidly progressive), hematuria, and proteinuria. Nephrotic syndrome was reported in three patients. Importantly, serum complements were depressed in only nine patients (41%).

On renal biopsy, (Table 1) mesangial proliferative glomerulonephritis was the predominant histologic pattern seen on light microscopy, reported in 13 patients (59%) and associated with focal crescent formation in three patients. Endocapillary proliferative glomerulonephritis was present in eight patients (36%), accompanied by prominent intracapillary neutrophil infiltration in six. All patients with endocapillary proliferative glomerulonephritis had low serum complements.[5,7–8] Necrotizing glomerulonephritis was seen in one patient. All seven patients with diabetes showed features of underlying diabetic glomerulosclerosis.[5,7] On immunofluorescence, IgA was the sole Ig deposited in

Table 1 | Clinical and pathological features of 22 previously reported cases of IgA-dominant APIGN

Ref	n	Age (years)	Staphylococcus species	Source of infection	Latent period (weeks)	Predisposing factors	Clinical presentation	Serum complement	Light microscopy	IgA deposits on IF	Location of deposit on EM	Treatment	Outcome
2	1	32	*S. aureus*	Empyema	10	None	Hematuria, proteinuria	Normal	MesPGN	Dominant	Mesangial	IV methicillin	Improved
3	5	21–65	MRSA	Abdominal abscess	5–16	Gall bladder cancer in one	RPGN and NS in one, RPGN in two, NS in two	Normal	MesPGN in four (two with crescents), necrotizing GN in one	Co-dominant	Not performed	Antibiotics	Three improved, one on HD, one died
4	1	71	MRSA	Pneumonia	1	Papillary carcinoma	Proteinuria, hematuria, renal failure	Normal	MesPGN	Dominant	Subepithelial, subendothelial, mesangial	Imipenem/ cilastatin	Improved
5	5	50–89	MSSA in three and *S. epidermidis* in two	Skin infection in four, rectal abscess in one	2–12	Diabetes	Acute on chronic RF	Depressed	PGN with neutrophils	Sole in three, dominant in two	Subepithelial in five, subendothelial in four, mesangial in five	Antibiotics	Four on HD, one recovered
6	1	48	MRSA	Pneumonia	2	Poor nutrition	NS, RF hematuria	Normal	MesPGN with crescents	Dominant	Subepithelial, mesangial	Steroids, antibiotics	Improved
7	8	60–80	Five MRSA/2 MSSA/1 S. *epidermidis*	Skin infection in three, endocarditis in one, surgical infectious complications in four	Not reported	Diabetes in two, sarcoma in one	ARF, heavy proteinuria, hematuria	Depressed in three, normal in five	MesPGN in six, PGN in two	Dominant in four, co-dominant in four	Mesangial in eight, intramembraneous in six, subendothelial in one	Antibiotics in all, steroids in one	Five HD, three improved
8	1	66	MSSA	Joint infection	<1	None	ARF, hematuria, proteinuria	Depressed	PGN with neutrophils	Co-dominant	Subendothelial, mesangial	Vancomycin	Improved
our case	1	67	MRSA	Pneumonia	3	Diabetes	Acute on chronic RF	Depressed	PGN with neutrophils	Dominant	Subepithelial, subendothelial, mesangial	Antibiotics	HD (expired)

ARF, acute renal failure; APIGN, acute post-infectious glomerulonephritis; EM, electron microscopy; HD, hemodialysis; IF, immunofluorescence; MesPGN, mesangioproliferative glomerulonephritis; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-sensitive *Staphylococcus aureus*; N, number of patients; NS, nephrotic syndrome; PGN, endocapillary proliferative glomerulonephritis; RF, renal failure; RPGN, rapidly progressive glomerulonephritis.

glomeruli in three patients and the dominant Ig in nine patients. In the remaining 10 patients, IgA staining intensity was similar to IgG. Co-deposition of C3 was present in all but one case. Electron microscopy was performed in 17 patients. Mesangial electron dense deposits were seen in all cases (100%), subepithelial deposits in seven (41%), subendothelial in seven (41%), and intramembranous in six (35%).

All 22 patients were treated with antibiotics and two also received steroids. Five patients (23%) had complete recovery of renal function with normalization of serum creatinine and, when reported, decreasing proteinuria to <300 mg/24 h urine collection. Six patients (27%) had partial recovery with moderate reduction of proteinuria and serum creatinine. The remaining 11 patients (50%) remained dialysis-dependent including one of the two patients treated with steroids.

In a large Italian study of 393 type II diabetic patients who underwent renal biopsy, Mazzucco *et al.*[9] found that membranous glomerulopathy, APIGN, and IgA nephropathy were the three most common nondiabetic glomerular diseases encountered. In their series, 70.3% of cases of APIGN in diabetic patients occurred superimposed on diabetic glomerulosclerosis. This likely relates to the fact that diabetic peripheral vessel disease and neuropathy, which predispose to skin ulcers and superimposed infection, are more common in diabetic patients with renal involvement.

In the setting of underlying diabetic nephropathy, the appearance of APIGN is different from that of pure APIGN. Differences include a predominance of mesangial and subendothelial electron dense deposits with only sparse and small subepithelial deposits, even during the active phase of diffuse endocapillary hypercellularity and neutrophil infiltration. It is likely that the underlying mesangial sclerosis and GBM thickening of diabetic glomerulosclerosis modify the morphological expression of the disease such that the immune deposits preferentially localize to the mesangium, possibly owing to defective mesangial clearing. The GBM thickening likely impedes the formation of large, hump-shaped subepithelial deposits.

We recently examined our experience with biopsies from patients with APIGN and diabetes mellitus received in the Renal Pathology Laboratory of Columbia University. Among the 18 cases identified, 16 (90%) occurred superimposed on diabetic glomerulosclerosis. Among the ones superimposed on diabetic glomerulosclerosis, 12 (75%) were associated with *Staphylococcus* infection, two (12.5%) with *Streptococcus* infection, and two with unknown pathogens. Of the 12 cases associated with *Staphylococcus*, eight (67%) were IgA-dominant on immunofluorescence (including five that were reported previously[5]). The other four cases (33%) showed diffuse endocapillary hypercellularity and neutrophil infiltration on light microscopy, glomerular immune deposits that stained for either IgG and C3 or C3 alone on immunofluorescence, and abundant mesangial and some subendothelial electron dense deposits with only rare subepithelial deposits on electron microscopy. Hence, at least from this small cohort, it appears that IgA-dominant poststaphylococcal glomerulonephritis may be the most common histological pattern of APIGN in patients with diabetic glomerulosclerosis.

The pathomechanism of the selective IgA deposition in patients with poststaphylococcal glomerulonephritis superimposed on diabetic nephropathy is unclear. It may relate to increased serum levels of IgA and IgA-containing circulating immune complexes in diabetics,[10–12] possibly as a result of subclinical mucosal infection or decreased IgA hepatic clearance caused by serum IgA1 hypersialylation.[13] Because most cases of IgA-dominant poststaphylococcal glomerulonephritis have been described in nondiabetic patients, this selective glomerular IgA deposition is more likely related to the *Staphylococcus* bacterium itself. Arakawa *et al.*[14] found that serum IgA titers against *S. aureus* cell membrane antigen are elevated. This group speculated that postmethicillin-resistant *S. aureus*-associated glomerulonephritis might be mediated by staphylococcal enterotoxin, which acts as a superantigen. Superantigen binds directly to the major histocompatibility class II molecule on antigen presenting cells without being internally processed. The superantigen/major histocompatibility class II complex then interacts with the variable portion of the beta chain ($V\beta$) of the T cell without major histocompatibility restriction, causing massive T-cell activation and production of high amounts of cytokines, including those with IgA class-switching functions.[3,14,15] Unknown staphylococcal cell surface antigens may also be implicated in mounting an IgA-dominant immune response as some of the reported cases of IgA-dominant APIGN were associated with *S. epidermidis,* which does not produce enterotoxin.[5,7] Interestingly, the same Japanese group recently detected *S. aureus* envelope antigen designated 'probable adhesin' on the glomeruli of 68% patients with IgA nephropathy and IgA-dominant methicillin-resistant *S. aureus*-associated glomerulonephritis.[16] Based on their findings, they speculated that this envelope antigen may be more widely implicated in the pathogenesis of IgA nephropathy. Of note, other bacterial antigens, like *Haemophilus parainfluenzae* outer membrane antigens, also have been previously detected in the glomeruli of patients of IgA nephropathy.[17]

IgA-dominant poststaphylococcal glomerulonephritis must be distinguished from IgA nephropathy. Findings that favor APIGN over IgA nephropathy or Henoch Schönlein purpura include hypocomplementemia, intercurrent culture-documented staphylococcal infection, diffuse endocapillary hypercellularity with prominent neutrophil infiltration on light microscopy, and subepithelial 'humps' on electron microscopy[18] (Table 2). This pathological distinction has important clinical implications because of the different treatments and prognoses of the two diseases. Current evidence suggests that IgA-dominant APIGN superimposed on diabetic nephropathy has a poor prognosis. Follow-up was available on seven of our eight cases of IgA-dominant APIGN superimposed on diabetic glomerulosclerosis, six of which have remained dialysis dependent. In contrast IgA nephro-

Table 2 | Features favoring IgA-dominant acute post-infectious glomerulonephritis over IgA nephropathy

Clinical features
1- Intercurrent culture-documented staphylococcal infection
2- Hypocomplementemia
Histological features
1- Endocapillary hypercellularity with neutrophil infiltration
2- Subepithelial "humps" on electron microscopy

pathy in the setting of diabetic nephropathy may have a relatively small impact on outcome.[19] It is important to note that in more then half of reported cases of IgA-dominant poststaphylococcal glomerulonephritis (Table 1), serum complements were normal, light microscopy revealed mesangial proliferation in the absence of endocapillary proliferation or neutrophil infiltration, and no subepithelial deposits were identified on ultrastructural evaluation. Thus, the distinction between IgA nephropathy and APIGN in these cases was very difficult, if not impossible.

In conclusion, staphylococcal infection has emerged as one of the leading causes of APIGN in adults. Three distinct patterns of APIGN can be seen, one of which has the distinct feature of containing deposits which appear IgA-dominant or co-dominant on immunofluorescence. The entity of IgA-dominant APIGN is commonly seen in patients with underlying diabetic glomerulosclerosis. It is important to distinguish this entity from IgA nephropathy because of the differences in treatment and prognosis.

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